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MANDELAMINE AND URINARY-TRACT INFECTIONS

Methenamine mandelate USP (Mandelamine - Warner, Chilcott), a compound of methenamine and mandelic acid, is a relatively old drug now being promoted for the treatment of chronic or resistant urogenital infections. The manufacturer correctly claims that "in sharp contrast to antibiotics and sulfonamides, Mandelamine may be used without risk of patient sensitization or bacterial resistance."

Because of the scarcity of clinical and bacteriological data on its effectiveness, Medical Letter consultants do not recommend Mandelamine as a first-choice antibacterial for urinary-tract infections. They do, however, regard it as a potentially valuable agent in many chronic infections in which antibiotics, sulfonamides and nitrofurantoin (Furadantin - Eaton) are ineffective or cannot be used because of toxic, allergic or other side effects. Unlike many other antibacterial drugs, Mandelamine can be given continuously over long periods; there is as yet no evidence of the emergence of resistant organisms.

ACIDIFICATION NEEDED - The drug has bacteriostatic effects on all common urinary pathogens, though B. proteus and Aerobacter aerogenes are somewhat less sensitive to it than E. coli, Staphylococcus aureus, enterococci and Pseudomonas aeruginosa. The antibacterial activity of the drug against all microorganisms is, however, critically dependent on a low urine pH. Mandelamine itself has some acidifying effect, but it is not likely to lower the pH sufficiently; a urine-acidifying agent must usually be used along with the drug, and the pH kept below 5.

Ammonium chloride, the most commonly used urine acidifier, will lower the pH to this level for only a few days; then the well-known compensatory production of ammonia by the renal tubules causes the pH of the urine to rise. Methionine NF is preferable to ammonium chloride as a urinary acidifier for prolonged use. Six to 12 grams daily in divided doses may be required for sustained lowering of the pH to 5 or less. Since methionine may cause gastrointestinal disturbance, the patient should be instructed to check the pH level daily with Nitrazine paper (Squibb), and to use no more methionine than is needed to keep the pH level below 5.

Proper acidity may be difficult to maintain in the presence of such urea-splitting bacteria as B. proteus; and urea-splitting organisms are becoming

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more frequent pathogens in urinary-tract infections (H. Seneca, et al., Ann. Int. Med., 53: 468, 1960). Where impaired renal function interferes with ammonia response, acidification of the urine to low pH values is more easily achieved, but patients with such impairment are easily thrown into clinical acidosis. Toxic reactions to Mandelamine are infrequent, though gastric and bladder irritation may occur.

DOSAGE - With all antibacterial agents used for urinary-tract infections, both dosage and duration of therapy should be individually determined. The usual dose of Mandelamine is four to six grams daily. In chronic infections, medication should be continued for at least three to six months, and often longer. With this drug, as with other antibacterial agents, quantitative bacterial cultures provide a much more reliable guide to both dosage and duration of treatment than ordinary qualitative urine cultures (E. H. Kass, Am. J. Med., 18: 764, 1955).

For a first attack of urinary-tract infection, almost any antibacterial drug is likely to give a satisfactory response, since the problem of drug resistance is usually of minor importance. In recurrent or chronic infections, urine-culture and sensitivity tests should be used to determine the appropriate antibacterial agent. The more soluble sulfonamides, sulfisoxazole (Gantrisin - Roche), sulfisomidine (Elkosin - Ciba), sulfamethizole (Thiosulfil - Ayerst) and sulfacetamide (Sulamyd - Schering) are generally preferred to other sulfonamides in treatment of urinary infections (C. R. Kleeman, et al., Medicine, 39: 3, 1960).

TISSUE LEVELS - Mandelamine, like Furadantin, does not penetrate tissue and it does not act on deep-seated infections, such as the interstitial foci in chronic pyelonephritis. Whether high tissue levels are actually needed in either acute or chronic urinary-tract infections is, however, a matter of controversy. Acute infections are likely to clear up whatever the treatment; chronic infections are at best difficult to cure. Many able clinicians believe that with antibiotics and sulfonamides, urinary-tract infections respond no better to the full doses required for high tissue levels than to the lower doses which give adequate urinary levels. Chronic infections are often maintained by urinary obstruction which should, if possible, be corrected. Even where a permanent cure cannot be achieved, keeping the urine free of bacteria is likely to be beneficial.

(For a comprehensive review of chronic urinary-tract infections, see the forthcoming Biology of Pyelonephritis, edited by Edward H. Kass and Edward L. Quinn, Little Brown & Co.)

ANTACIDS IN ULCER THERAPY

The use of antacids to neutralize gastric acidity, along with dietary measures, is generally accepted as indispensable to effective treatment of peptic ulcer, though anticholinergics, sedation and psychologic support by the physician may also be helpful. Authorities differ as to the required dosage of antacids, but many hold that large doses must be taken frequently for adequate control of hyperacidity; these experts believe that haphazard or small doses - even if they relieve

symptoms - are of little value in achieving remission (M. J. Grossman, Clin. Res., 8:125, 1960). Smaller doses are, of course, useful for the relief of hyperacidity in the absence of active ulceration.

CHOICE OF ANTACID - Sodium bicarbonate is an excellent antacid, but repeated use may cause systemic alkalosis, especially if there is vomiting, and it has been largely discarded in chronic disorders such as peptic ulcer. The most popular antacid preparations contain aluminum hydroxide gel, alone or in combination with laxative agents. Large - and expensive - amounts of these preparations would be required for intensive neutralization in active peptic ulcer; the amounts actually used are generally much smaller.

Calcium carbonate is an excellent antacid for many patients (M. Brody and W. H. Bachrach, Am. J. Dig. Dis., 4:435, 1959; J. B. Kirsner, et al., Ann. Int. Med., 35:785, 1951). It acts more rapidly than other antacid compounds, generally exerting its full neutralizing effect before it is discharged from the stomach. Of the many antacids studied by Brody and Bachrach, the two that were lowest in cost in terms of equivalent in vitro neutralization were Albermag, a liquid preparation, and Albertabs, the equivalent tablet form, both calcium carbonate preparations manufactured by the Alborin Corp. of Los Angeles. The dosage required for intensive neutralization would be about 1 tablespoonful of the liquid or 3 tablets (3 Gm. of calcium carbonate) taken every hour. Drug stores are unlikely to stock either preparation, but they can be ordered by the druggist. The cost of Albermag is $1 for 12 oz., and of Albertabs, $1.50 per hundred. Other more readily available calcium carbonate preparations are Alkets Tablets (Upjohn) ($1.98 per hundred) and Titralac Liquid (Schenley) ($2.83 for 8 oz.). Albermag, Albertabs and Alkets contain magnesium compounds for laxative effect.

CALCIUM CARBONATE USP - A less expensive alternative is the purchase in bulk of precipitated calcium carbonate USP; and, if needed for laxative effect, magnesium carbonate USP, magnesium oxide USP, or magnesium trisilicate USP. A generous half teaspoonful (about 3 Gm.) of calcium carbonate generally maintains the gastric pH above 3 - a satisfactory level - for about 45 minutes. Some patients find a suspension of calcium carbonate in water more palatable than the popular aluminum hydroxide preparations. A pound of precipitated calcium carbonate USP costs about $1.50 to $2 (about a penny for a 3-Gm. dose). For laxative effect, magnesium oxide may be mixed with the calcium carbonate in the ratio of about 5 heaping teaspoonfuls per pound. Not all patients, however, can safely or successfully use calcium carbonate for the prolonged therapy usually needed. It is contraindicated in patients with renal failure, where repeated large doses may cause systemic alkalosis or hypercalcemia. And while the formation of urinary calculi is an infrequent complication, calcium carbonate should not be used by patients with a tendency to calcium-stone formation.

Some patients may prefer one of the aluminum hydroxide or aluminum-magnesium hydroxide preparations to calcium carbonate even where the latter is effective. Creamalin liquid and Tricreamalate liquid (Winthrop) and Maalox liquid (Rorer) are among the preparations of this type which Brody and Bachrach found least expensive in terms of in vitro neutralizing ability. The cost of Creamalin and Tricreamalate is $1.95 for 16 oz., and of Maalox, $1.75 for 12 oz.

Some aluminum hydroxide preparations have been shown in animals to provide a protective coating for the gastric mucosa. Even if coating occurs in man, its therapeutic significance is doubtful. Milk given at short, regular intervals remains an excellent neutralizer; if undesirable weight gain occurs, the milk may be skimmed without loss of effectiveness.

OTRIVIN

Xylometazoline hydrochloride (Otrivin - Ciba), a topical sympathomimetic nasal vasoconstrictor chemically related to naphazoline hydrochloride (Privine - Ciba), is promoted "for gentle relief of stuffy nose, safe even for the very young." Its action is said to be prolonged, without rebound congestion and with minimal local or systemic side effects. Several uncontrolled studies in patients with vasomotor, allergic or infectious rhinitis, sinusitis, and serous otitis media are cited to support these claims. Similar claims, backed by similar evidence, have been made for Otrivin's many predecessors; yet none has proved clearly superior in effectiveness or safety to ephedrine or phenylephrine. Whether the new product will ultimately show any superiority remains to be determined.

Vasoconstrictors do have a genuine usefulness in giving temporary relief from stuffiness; and they may facilitate drainage from the sinuses or improve patency of the eustachian tubes. They do not combat infection, however, and they may actually encourage it by interfering with ciliary action or with the mucous film. With Otrivin, as with other vasoconstrictors, claims of safety are likely to encourage excessive dosage. And since mucous membranes are actively absorbent, especially when inflamed, enough of the drug may be absorbed to cause such systemic effects as nervousness, tremor, and palpitation.

SIDE EFFECTS - Excessive dosage or continued regular use of vasoconstrictors leads to diminished response, rebound congestion, or hyperemia of the mucosa, and finally to severe chronic rhinitis with swollen, pale membranes, stuffiness, and profuse nasal discharge resembling allergic rhinitis. Severe reactions, including ulceration of the mucosa, have occurred with Privine, and it has yet to be established that Otrivin is less likely to have such effects. Until more is known about side effects, Medical Letter consultants recommend the use of either 0.25% phenylephrine USP in isotonic solution (Neo-Synephrine - Winthrop) or 1% ephedrine in isotonic solution. With any nasal vasoconstrictor, the patient should be cautioned against overdependence on the drug.

Convenient plastic spray-packs are now widely used in place of the dropper. The patient should be instructed to apply the spray, wait a few minutes for the anterior portion of the nose to clear, and then apply it again. Drops may not be effective unless the head is maintained in the hyperextended position for several minutes. There is no convincing evidence that the addition of antibiotics, sulfa drugs, steroids or antihistamines to nasal vasoconstrictors improves ventilation of the nasal passages, reduces inflammatory responses, or controls the virus or bacterial infection causing the nasal congestion. In severe bacterial infections of the nose and throat, antibiotics or sulfonamides suited to the specific infection should be administered by mouth or parenterally.

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